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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,781	02/06/2001	Jacques Theze	202930US0CIP	3255

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
MERTZ, PREMA MARIA	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/776,781	Applicant(s) Theze et al.
	Examiner Prema Mertz	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 6, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above, claim(s) *1-15 and 17* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *16 and 18-26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group XVI (claims 16, 18, 19-26, drawn to a peptide of SEQ ID NO:6 or 8) in Paper No.12 (2/6/03) is acknowledged.

The traversal is on the ground(s) that the restriction is improper since the examiner has not shown that examination of the peptide of Group XV with the peptide of Group XVI, would entail a serious burden. This is not found persuasive because the searches for the two Groups would not overlap. The test for propriety of restriction is not whether the inventions are related but rather whether they are distinct and whether it would impose a burden on the examiner to search and examine multiple inventions in a single invention.

The inventions of Groups XV-XVI are products which are structurally and chemically different. Furthermore, a search of the peptide of amino acid sequence set forth in SEQ ID NO:6 would not be expected to reveal art directed to the other peptide of amino acid sequence set forth in SEQ ID NO:2 or 4.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP. § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP. § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

The Groups as delineated in the restriction requirement (Paper No. 11, 1/8/03) are patentably distinct one from the other such that each invention could, by itself, in principle, support its own separate patent (as shown by the arguments put forth in the written restriction requirement).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-15, 17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

2. There is no "Brief Description of the Drawings" on page 6, line 13. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 16, 18-26, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and in such a way as to enable one skilled in the art to which it pertains

The instant specification fails to adequately describe and enable peptides that are homologous to the peptides of SEQ ID NO:6 and 8. Applicants do not teach which regions of

said peptides are critical to the functions of the peptides. The specification does not provide the requisite examples nor a representative number of different sequences that would allow the skilled artisan to produce a peptide that is homologous to SEQ ID NO:6 or 8 having the substitutions as recited in claims 16, 19-25, nor does the disclosure provide criteria that explicitly enable such critical features. There is no guidance in the specification as to how one of ordinary skill in the art would generate the peptides, other than that exemplified.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim 16, 19-25 are genus claims. Claim 16 recites "homologous sequence thereof" and "one or more conservative changes" which limitations encompass peptide variants of SEQ ID NO:6 and 8. The term "conservative changes" or "homologous sequence" encompasses variants which means a peptide having one or more amino acid substitutions, deletions, insertions and/or additions made to the peptide molecule of amino acid sequence set forth in SEQ ID NO:6 or 8. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the nucleic acid molecule. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the

art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a peptide set forth in SEQ ID NO:6 or 8 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus of protein molecules.

Therefore only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:6 or 8, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. As a result, it does not appear that the inventors were in possession of "homologous" peptides or peptides with "conservative changes" i.e. variants of a peptide of SEQ ID NO:6 or 8.

Claims 16, 19-26 are also drawn to peptide homologues of the peptides of SEQ ID NO:6 or 8. The specification provides only sequence data to allow one to characterize the protein of SEQ ID NO:6 or 8, which are human peptides. Many distinct proteins may share the same activity, so that the biological activity of the claimed human peptide, stimulation of proliferation of IL-2 dependent TSIβ cell line (see pages 41-42, Example 11), may be a characteristic of many

distinct peptides not contemplated by the instant invention. As a result, if one were to synthesize a peptide from a different species that had the same activity, one could not reasonably predict if the isolated peptide was a species homologue of the original peptide because one could not determine if the sequence difference between the original and isolate were due to species differences or to the peptides being non-homologous but sharing the same activity. Even though assays are provided to test for possible activities (see pages 41-42), it would be undue experimentation to conduct every assay in the hopes of identifying a specific peptide having the desired activity, and no guidance is provided to enable a skilled artisan to predict which peptide that is "homologous" is likely to have the desired activity. There is no information about how to identify a suitable "homologous" peptide. Additionally species homologues often display low sequence identity so that identification based solely on sequence similarity is impossible. Under such common circumstances, if one cannot test for the expected activity of the encoded putative species homologue, then it is impossible to identify species homologues. For example in The Cytokine Facts Book (1994), Robin Callard and Andy Gearing. Academic Press Inc. San Diego, CA, the amino acid sequence of IL-2 (interleukin-2) from human compared to mouse differs by 16 amino acids in length (page 39, table) and share only about 60% identity (page 39, "Crossreactivity" section). Based solely on sequence, it would be clearly impossible for one skilled in the art to identify the mouse and human proteins as species homologues; however, when one is able to compare a known or putative activity (page 39, "Bioassays" section"), identity can be confirmed.

Furthermore, Reeck et al. (line 1-2) point out, ""Homology" has the precise meaning in biology of "having a common evolutionary origin,"...".

It is stated at the top of column 2 that:

A similarity, then, can become a fully documented, simple fact. On the other hand, a common evolutionary origin must usually remain a hypothesis, supported by a set of arguments that might include sequence or three-dimensional similarity. Not all similarity connotes homology but that can be easily overlooked if similarities are called homologies. Thus, in this third case, we can deceive ourselves into thinking we have proved something substantial (evolutionary homology) when, in actuality, we have merely established a simple fact (a similarity, mislabeled as homology). Homology among similar structures is a hypothesis that may be correct or mistaken, but a similarity itself is a fact, however, it is interpreted.

Reeck et al. provided emphasis to the above reasons for not being able to identify, if one is able to isolate candidates, species homologues as claimed because of the lack of guidance and information in the current specification. Thus, at the time the application was filed, a homologous peptide that differs from SEQ ID NO:6 or 8 by one or more conservative changes, was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention.

3b. Claims 16, 18-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide consisting of the amino acid sequence set forth in SEQ ID NO:6 or 8, does not reasonably provide enablement for a peptide as set forth in claims

16, 18-26. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 16, 18-26 encompass peptide variants of the peptides of SEQ ID NO:6 or 8, which claims are overly broad, since no guidance is provided as to which of the myriad of peptide molecules encompassed by the claims will retain the characteristics of the desired peptides. Variants of the peptide can be generated by conservative or nonconservative changes, allelic, splice species or polymorphic variants. However, Applicants have failed to disclose any actual or prophetic examples on expected performance parameters of any of the possible peptide muteins of SEQ ID NO:6 or 8. Moreover, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid

shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the specification as to how one of ordinary skill in the art would generate peptides other than those exemplified in the specification. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 16, 18-26, in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim rejections-35 USC § 112, second paragraph

4. Claims 16, 18-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is unclear for several reasons.

Claim 16 is indefinite in the recitation of the term "IP131". The recitation of this term in the claims is vague and indefinite. It is suggested that the recitation of this term be deleted from the instant claim. Similarly claim 18 is indefinite in the recitation of the term "IP131".

Claim 16 is unclear because it recites "one or more" conservative changes, which limitation encompasses changing every single amino acid to another amino acid. Therefore, the metes and bounds of the claim are unclear.

Claim 16 recites "substantially the same activity or binding characteristics" which is vague and indefinite. It is unclear how substantial the activity and binding characteristics should be, is it 75% similar, 90% similar or even 99% similar. Furthermore, the recitation of "activity" itself in the claim is unclear, and it is also unclear what "binding characteristics" are being referred to in the claim. It is suggested that the claims be amended to recite the specific activity and binding characteristic disclosed in the specification (see pages 41-42, Example 11).

Claims 19-26 are rejected as vague and indefinite insofar as they depend on the above rejected claims for their limitations.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz

Prema Mertz Ph.D.
Patent Examiner
Art Unit 1646
March 11, 2003